REMARKS/ARGUMENTS

The Office Action and Applicant's Response to Supplemental Restriction Requirement

The Examiner acknowledged Applicant's previous election of Group II in response to a restriction requirement issued July 17, 2002, and Applicant's cancellation of non-elected subject matter.

The Examiner stated that "[t]he Office has determined that, through inadvertent error, the Office action mailed July 17, 2002 requiring restriction did not properly distinguish subject matter contained in the previously identified Groups I-III that is considered to be directed to distinct inventions as defined below." Accordingly, the Examiner issued a supplemental restriction requirement, under 35 U.S.C. § 121, and required Applicant to elect a single invention to which the claims must be restricted. The Examiner designated two claim groups.

I. Claims 1-11, 15, 43-45, 47, and 49-60 drawn to an in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell; and a kit for transdifferentiating, in vitro, an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell.

II. Claims 17, 19, 22, 23, 27-30, 33-36, 39, and 61-66 drawn to a transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell produced by the method; and a cell culture derived from the transdifferentiated cell produced by the method.

The Examiner asserted the following basis for the supplemental restriction requirement:

In the instant case the cells of group II can be made by transfecting basal epidermal cells with a vector containing one of the immunologically detected proteins. Such a process has no steps in common with the claimed methods, and would result in a cell of epidermal origin, cultured in vitro, that would possess the requisite features claimed by applicant.

Applicant strongly disagrees with the Examiner's assertion and traverses the supplemental restriction requirement. The process suggested by the Examiner would fail to produce the "a transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell *produced by the method.*"

However, as required by 37 C.F.R. § 1.143, Applicant provisionally elects designated claim **Group I**, with a full reservation of rights under 35 U.S.C. § 121.

First, Applicant presumes that the Examiner intended that the *expression* vector contains *a gene encoding* one of the immunologically detected proteins. If the Examiner has another process in mind, Applicant respectfully requests to be corrected. A cell produced by the method presumably proposed by the Examiner might indeed be expected to express one of the immunologically detected proteins, however its gene expression profile and overall phenotype would differ dramatically from a cell produced by the claimed methods in designated claim group I. This is because the claimed method by which the claimed cells and cell cultures are produced includes, *inter alia*, the following steps (e.g., Claims 1 and 49):

> . . . (b) exposing the cell(s) to an amount of an antagonist of bone morphogenetic protein (BMP) effective to antagonize endogenous BMP signal transduction activity;
>
> (c) growing the cell(s) in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or a segment of a human HES1 gene, or homologous non-human counterpart of either of these, in an amount effective to suppress the expression of functional gene product of MSX1 and/or HES1, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell; and
>
> (d) growing the transdifferentiated cell in a medium comprising a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), platelet derived growth factor (PDGF), nerve growth factor (NGF), sonic hedgehog, sonic hedgehog aminoterminal peptide, neurotrophin (NT)-3, and neurotrophin (NT)-4 . . .

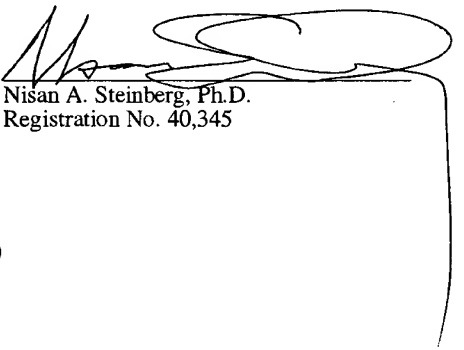
Consequently, the claimed cell produced by the claimed method, in contrast to a cell produced by the process presumably suggested by the Examiner, is subject to antagonism of BMP signal transduction activity and suppression of MSX1 and/or HES1 expression. (See, e.g., specification at page 2, line 28 through page 4, line 4). This results in a cell with a phenotype substantially and detectably different from an epidermal basal cell that is merely transfected with an expression vector bearing a gene encoding a marker characteristic of a neuronal cell, as proposed by the Examiner, in which cell BMP-mediated signal transduction and MSX1 and/or HES1 expression continue to occur and mediate the induction of a cascade of detectable gene

products. The Examiner's hypothetical cell would consequently possess a gene expression profile substantially different from that of the cell as claimed by Applicant.

In addition, by "growing the transdifferentiated cell in a medium comprising a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), platelet derived growth factor (PDGF), nerve growth factor (NGF), sonic hedgehog, sonic hedgehog aminoterminal peptide, neurotrophin (NT)-3, and neurotrophin (NT)-4," in accordance with the method as claimed in, e.g., step (d) of Claims 1 and 49, substantial phenotypic differences would be readily detectable between the claimed cell and the cell made by the Examiner's proposed process. For example, as recited, e.g., in Claims 35 and 49, a detectable "morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length," which would not be a phenotype expected in the Examiner's hypothetical cell; neither would a GABAergic (e.g., Claims 22 and 33) nor dopaminergic (e.g., Claims 23 and 34) phenotype be expected in the Examiner's hypothetical cell.

Since, the cell produced by the claimed method would not be the same as the cell made by the Examiner's proposed method, Applicant respectfully submits that the supplemental restriction requirement is improper and requests that the Examiner reconsider and withdraw this restriction requirement, rejoining designated claim groups I and II..

Respectfully submitted,



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